Godina 2016. u kardiologiji: periferna cirkulacija

The year in cardiology 2016: peripheral circulation

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Uvod

Prema najnovijim epidemiološkim podatcima, procjenjuje se da kardiovaskularne (KV) bolesti uzrokuju 45 % smrtnosti u Europi, uključujući 12 % moždanih udara i 14 % drugih cerebrovaskularnih događaja, upozoravajući na veliku ulogu nekoronarne arterijske bolesti (aorte, karotida i arterija donjih udova) i venskog tromboembolizma (DVT) (**Figure 1**).[1] Slično prethodnim godinama,[2,3] relevantni znanstveni dokazi u ovom području izneseni su i u 2016. godini i oni će utjecati na svakodnevnu kliničku praksu.

Bolest karotidnih arterija

U novim Europskim smjernicama za prevenciju kardiovaskularnih bolesti u kliničkoj praksi iz 2016. godine znatno se promijenila uporaba mjerenja zadebljanja intime i medije karotidnih arterija za stratificiranje KV rizika i taj biljeg više

Preamble

In an epidemiological update in 2016, cardiovascular (CV) disease has been estimated as cause of 45% of deaths in Europe, including 12% due to stroke and 14% to other CV diseases, highlighting the major burden of non-coronary artery diseases (i.e. aorta, carotid, and lower extremity arteries) and venous thromboembolism (VTE) in our continent (**Figure 1**).[1] Similar to previous years,[2,3] relevant scientific evidence in these fields was brought out in 2016 which will affect our daily clinical practice.

Carotid artery disease

In the new '2016 European guidelines on cardiovascular disease prevention in clinical practice', the usefulness of carotid intima-media thickness to stratify CV risk has been strikingly challenged, and this marker is no longer recom-

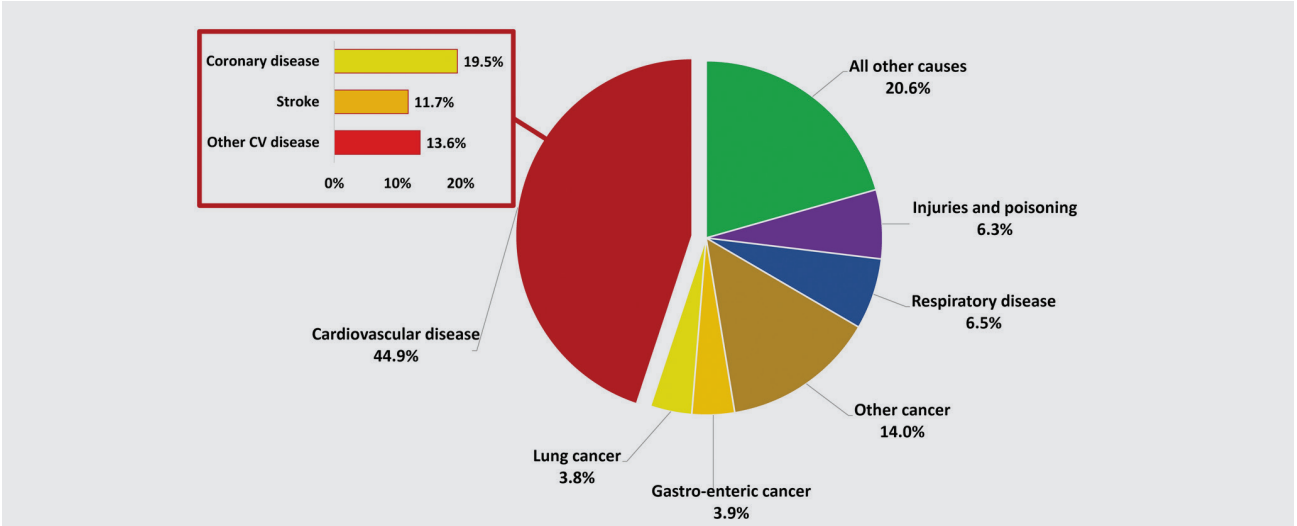

FIGURE 1. Proportion of all deaths due to major causes in Europe, latest available year (adapted from Townsend).[1]
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nije preporučen s obzirom na njegovu visoku varijabilnost, individualno nisku reproducibilnost i nedostatak prediktivne dodane vrijednosti, čak i u osoba umjerenog rizika.[4] Suprotno tomu, karotidni plakovi ostaju važno pomagalo za stratifikaciju KV rizika.

U 2016. godini dugoročna klinička ravnoteža u praćenju stentiranja karotidnih arterija (CAS) u odnosu prema karotidnoj endarterektomiji (CEA) potvrđena je 10-godišnjom analizom u studiji CREST (*Carotid Revascularisation Endarecteromy vs. Stenting Trial*), gdje analiza pokazuje sličnu učestalost smrtnosti, moždanih udara, infarkta miokarda unutar 30 dana, ili ipsilateralnog moždanog udara do 10 godina za obje strategije (11,8 % prema 9,9 %; P = 0,51) (**Tablica 1**).[5]

Periproceduralni moždani udar tijekom CAS-a obično je povezan s embolizacijom plaka. Randomizirana studija ACT (Asymptomatic Carotid Trial) usporedila je CAS s protekcijom od embolizacije u usporedbi s CEA-om u 1453 bolesnika s asimptomatskom karotidnom stenozom, koji nisu uzeti u obzir zbog visokoga kirurškog rizika (**Tablica 1**).[6] Zajednički primarni cilj od zbroja smrtnih ishoda, moždanih udara, infarkta miokarda unutar 30 dana, ili ipsilateralnog moždanog udara unutar 1 godine upozorio je na neinferiornost intervencijskog postupka (CAS) u usporedbi s kirurškom CEA (3,8 % prema 3,4 %; P = 0,01 za neinferiornost); no ipak, učestalost periproceduralnih moždanih udara favorizira CEA (1,4 % prema 2,8 % za CAS; P = 0,23). U 2016. godini tri mala prospektivna registra izvijestila su o nižoj učestalosti periproceduralnih moždanih udara, 0 – 0,9 %, s novim dvostruko obloženim karotidnim stentovima.[7-9]

Dok kirurško liječenje ostaje postupak izbora, postavlja se pitanje stratifikacije rizika u bolesnika s asimptomatskom karotidnom stenozom koji bi imali koristi od revaskularizacije.

Bolesti aorte

Muticentrična studija NORRE (*Normal Reference Ranges for Echocardiography*) iznijela je referentne varijable za ehokardiografska mjerenja, uzimajući u obzir različite konvencije mjerenja i vrijeme srčanog ciklusa.[10] Referentne se vrijednosti uzimaju u obzir i za sportaše, kao što je prikazano u studiji na 3281

mended due to its high variability, low intra-individual reproducibility, and lack of added predictive value, even in intermediate risk subjects.[4] In opposition, carotid plaque remains a valuable tool for CV risk stratification.

In 2016, the long-term clinical equipoise of carotid artery stenting (CAS) vs. carotid endarterectomy (CEA) was confirmed by the 10 year analysis of the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST), reporting similar rates of death, stroke, or MI within 30 days, or ipsilateral stroke up to 10 years for both strategies (11.8% vs. 9.9%; *P* = 0.51) (**Table 1**).[5]

Peri-procedural stroke during CAS is often related to plaque embolization. The randomized Asymptomatic Carotid Trial (ACT) I compared CAS with embolic protection to CEA in 1453 patients with asymptomatic carotid stenosis, not considered at high surgical risk (**Table 1**).[6] The composite endpoint of death, stroke, or MI at 30 days, or ipsilateral stroke at 1 year, was non-inferior in CAS vs. CEA (3.8% vs. 3.4%; *P* = 0.01 for non-inferiority); however, peri-procedural stroke rates numerically favoured CEA (1.4% vs. 2.8% for CAS, *P* = 0.23). Notably, in 2016, three small prospective registries reported peri-procedural stroke rates as low as 0–0.9% with the new dual-layered carotid stents, consisting of a thin-strut nitinol stent covered with a nitinol mesh.[7-9]

While surgery remains the procedure of choice, the pending question is the risk stratification of patients with asymptomatic carotid stenosis who would benefit from revascularization.

Aortic diseases

The multicentre Normal Reference Ranges for Echocardiography (NORRE) study provided reference values for echocardiographic measures, taking into account different measurements conventions, and timing of the cardiac cycle.[10] Normal values apply also to athletes, as shown by a study on 3281 healthy elite athletes which reported that 1.8% of men and 1.5% of women had ascending aorta diameters >40 mm and 34 mm, respectively.[11] Important data were recently published

TABLE 1. Summary of major randomized trials in the aorta, peripheral artery diseases, and venous thrombo-embolic disease in 2016.

Trial	Type and aim	Challenger	Reference	N	Setting (indication)	Primary endpoint	Main hypothesis validated?
Carotid arteries							
ACT-1[6]	Open: non-inferiority (3% margin) of CAS vs. CEA	CAS	CEA	1453	Asymptomatic patients at average surgical risk	Death, stroke, or MI within 30 days, or ipsilateral stroke up to 1 year	Yes
CREST (10 years)[5]	Open: superiority of CAS vs. CEA	CAS	CEA	2052	Symptomatic or asymptomatic carotid stenosis	10 year composite of any stroke, MI, or death	No
Aorta							
AARDVARK[24]	Single blind: perindopril vs. amlodipine vs. placebo to reduce AAA growth	Perindopril 10 mg OD	Amlodipine 5 mg OD or placebo	224	Patients with AAA (30–54 mm)	Change in AAA diameter	No
Lower extremity artery disease							
EUCLID[25]	Double blind: superiority of ticagrelor vs. clopidogrel in PAD patients	Ticagrelor 90 mg BID	Clopidogrel 75 mg OD	13 885	ABI ≤0.80 or prior revascularization	Efficacy: composite of CV death, MI, or stroke at 3 years	Efficacy: no
						Safety: major bleeding	Safety: yes
EUCLID prior revascularization subgroup[26]	Double blind: superiority of ticagrelor vs. clopidogrel in LEAD patients	Ticagrelor 90 mg BID	Clopidogrel 75 mg OD	7875	Prior revascularization	Efficacy: composite of CV death, MI, or stroke at 3 years; acute limb ischaemia	Efficacy: no
						Safety: major bleeding	Safety: yes
TRA2°P—qualifying LEAD subgroup[27]	Double blind: superiority of vorapaxar vs. placebo on top of aspirin and/or thienopyridine	Vorapaxar 2.5 mg OD	Placebo	3787	Claudicants with ABI ≤0.85 or prior revascularization	Efficacy: acute limb ischaemia up to 3 years	Efficacy: yes
						Safety: severe bleeding	Safety: yes
TRA2°P—known LEAD subgroup[28]	Double blind: superiority of vorapaxar vs. placebo on top of aspirin and/or thienopyridine	Vorapaxar 2.5 mg OD	Placebo	5845	Claudicants with ABI ≤0.85 or prior revascularization	Efficacy: peripheral revascularization up to 3 years	Efficacy: yes
						Safety: severe bleeding	Safety: yes
IN.PACT SFA I (3 years)[29]	Open: superiority of DEB vs. PTA for FP lesions	DEB	PTA	331	Rutherford class 2 to 4 FP lesions	Efficacy: 3 year primary patency; freedom from CD-TLR	Efficacy: yes
						Safety: death, clinically driven TVR, major amputation, thrombosis	Safety: yes
ZILVER PTX (5 years)[30]	Open: superiority of DES vs. PTA for FP lesions	DES	PTA	474	Rutherford class 2 to 6 FP lesions	5 year primary patency; freedom from CD-TLR	Yes
Venous thrombo-embolic disease							
CACTUS[37]	Open; superiority of 6 week nadroparine vs. placebo in low-risk patients with symptomatic calf DVT	nadroparine 171 UI/kg OD	Placebo	259	Symptomatic first isolated distal DVT event	Efficacy: composite of proximal DVT extension, contralateral DVT, and PE	Efficacy: no
						Safety: bleedings	Safety: no

AAA, abdominal aortic aneurysm; CAS, carotid artery stenting; CD, clinically driven; CEA, carotid endarterectomy; DEB, drug eluting balloon; DVT, deep vein thrombosis; FP, femoro-popliteal; LEAD, lower-extremity artery disease; MI, myocardial infarction; PE, pulmonary embolism, PTA, percutaneous transluminal angioplasty; TLR, target lesion revascularization; TVR, target vessel revascularization.

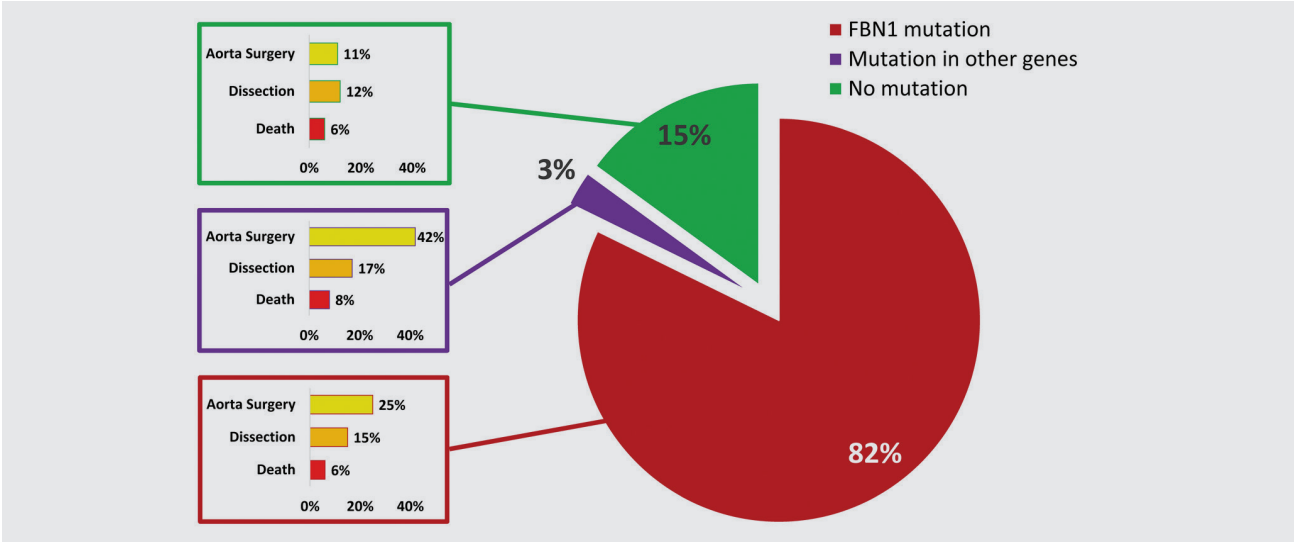

FIGURE 2. Prevalence of genetic abnormalities and outcomes according to subgroups in the Dutch CONgenital CORvitia registry (adapted from Franken).[15]

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zdravom profesionalnom sportašu, gdje 1,8 % muškaraca i 1,5 % žena imaju promjer ascendentne aorte >40 mm i 34 mm.[11] Važni podatci nedavno su objavljeni s obzirom na procjenu rizika od disekcije aorte (AD) u osoba s umjerenom dilatacijom ascendentne aorte.[12] Među 4654 osobe petogodišnji rizik od AD-a i/ili rupture bio je 0,4 %, 1,1 %, i 2,9 % kod promjera aorte od 45 mm, 50 mm i 55 mm. Stoga nalaz dilatacije korijena aorte indicira potrebu rada na osnovnom stanju i planiranju monitoringa.

Važni su koraci poduzeti u razumijevanju genetike bolesti aorte. Identificiranje gubitka funkcije mutacije u genima liziloksidaze (LOX), koja je uključena u regulaciju stabilnosti i integritet elastina i kolagena, u obiteljima s nasljednom predispozicijom za bolest torakalne aorte.[13] Postojanje humane mutacije LOX-a u mišjem genomu uzrokuje aneurizmu ascendentne aorte i spontanu hemoragiju u miševa koji su homozigoti za humane alele, vjerojatno putem nedostatne križne povezanosti elastina i kolagena u stijenci aorte.[14]

Utjecaj genotipa na težinu aortnog fenotipa prikazan je u rezultatima iz registra *Dutch CONgenital CORvitia* u bolesnika s Marfanovim sindromom (MFS) (**Slika 2**).[15] Među 357 pacijenata s mutacijom fibrilin-1 gena, oni koji imaju mutaciju koja dovodi do reducirane količine proteina fibrilin-1 imaju lošiju 8-godišnju prognozu nego oni s dominantno negativnim mutacijama (produkcija abnormalnog proteina fibrilina-1), s 2,5 puta, 2,4 puta, i 1,6 puta povećanim rizikom od kardiovaskularne smrtnosti, smrti ili disekcije aorte, i bilo koje aortne komplikacije.

Drugi prognostički podatci prikazani su analizom podataka iz registra *GenTAC* koji je uključio 1991 pacijenta s genetski povezanom aneurizmom torakalne aorte (TAA).[16] Tijekom prosječnog praćenja od 3,6 godina 1,6 % pacijenata doživjelo je AD tip A, a samo u 13 % veličina aorte odgovarala je kriterijima smjernica za TAA zahvat. No, MFS donosi 7 puta veći rizik od AD. Drugi izvještaj iz registra *GenTAC* donosi ishode 94 žena s MFS-om s ukupno 227 trudnoća, prema kojima je 10,6 % žena imalo s trudnoćom povezanu aortnu komplikaciju s 8 puta većim rizikom od AD-a.[17]

U AD-u tipa B standardna skrb kod nekompliciranih slučajeva jesu medikamentno liječenje i torakalni endovaskularni

regarding the assessment of the risk of aortic dissection (AD) in subjects with moderately dilated ascending aorta.[12] Among 4654 individuals, the 5 year risk of AD and/or rupture was 0.4%, 1.1%, and 2.9% at baseline aortic diameters of 45 mm, 50 mm, and 55 mm, respectively. Therefore, the finding of aortic root dilatation indicates the need for a work-up of underlying conditions and scheduled monitoring.

Important steps in the understanding of genetic aortic diseases have been taken. In particular, loss-of-function mutations in lysyl oxidase (LOX) genes, involved the regulation of the stability and integrity of elastin and collagen, were identified in families with inherited predisposition for thoracic aortic diseases.[13] Introducing a human LOX mutation in the mouse genome caused ascending aortic aneurysm and spontaneous haemorrhage in mice that were homozygous for the human allele, likely through insufficient cross-linking of elastin and collagen in the aortic wall.[14]

In patients with Marfan syndrome (MFS), the impact of genotype on aortic phenotype severity was demonstrated in the Dutch CONgenital CORvitia registry (**Figure 2**).[15] Among 357 patients with mutations of the fibrillin-1 gene, those with mutations causing reduced amount of fibrillin-1 protein had a worse 8 year prognosis than those with dominant-negative mutations (production of abnormal fibrillin-1 protein), with 2.5-fold, 2.4-fold and 1.6-fold increase in the risk of cardiovascular mortality, death or aortic dissection, and any aortic complication, respectively.

Other prognostic data were reported from the GenTAC registry, including 1991 patients with genetically associated thoracic aortic aneurysms (TAA).[16] During an average follow-up of 3.6 years, 1.6% of patients experienced type-A AD; however, only 13% met the guideline criteria on aortic size for TAA repair. Importantly, MFS conferred a seven-fold increase in the risk for AD. Another report from the GenTAC registry described the outcome of 94 women with MFS who had a total of 227 pregnancies, reporting 10.6% pregnancy-related aortic complication rates, with eight-fold increased risk for AD.[17]

aortni zahvat (TEVAR) kod kompliciranih slučajeva. No, nedavna retrospektivna studija na 338 pacijenata s nekompliciranom AD tipa B usporedila je TEVAR (n = 184) s medikamentnim liječenjem (n = 154) i pokazala da je 30-dnevni mortalitet sličan, no bolesnici liječeni samo farmakološki imali su u petogodišnjem praćenju mnogo višu smrtnost (p = 0,001) i s aortom povezane neželjene događaje (p = 0,025).[18] Druga retrospektivna studija na 156 pacijenata s AD-om nekompliciranog akutnog tipa B identificirala je aortni promjer >44 mm kao neovisni prediktor smrtnosti tijekom praćenja od 3,7 godina; aortni promjer >44 mm i promjer lažnog lumena >22 mm povezani su s razdobljem bez intervencije.[19] Ovi podatci pridonose identifikaciji visokorizičnih kriterija koji favoriziraju potrebu ranog liječenja primjenom TEVAR-a.

Česta komplikacija vezana uz TEVAR jest postimplantacijski sindrom (PIS) – definiran kao temperatura >38 °C, leukociti >12,0/nL i CRP >10mg/dL tijekom 72 sata nakon implantacije unatoč negativnoj hemokulturi. O njemu je izvješteno u 16 % slučajeva AD-a tipa B; PIS nije utjecao na ishod bolničkog liječenja, ali je povezan s povećanom stopom važnih neželjenih događaja (smrt, ruptura aorte ili potreba za ponovnom intervencijom) u četverogodišnjem praćenju (62,5 % prema 25,9 %; P = 0,004).[20]

Ultrazvučni probir na aneurizmu abdominalne aorte (AAA) preporučen je u svih muškaraca >65 godina (klasa preporuke I A) i u žena koje su pušači i u dobi >65 godina (klasa preporuke IIb C).[21] Finska studija na 585 pacijenata s rupturiranom AAA postavila je pitanje o ovim preporukama, s obzirom na to da je 21 % muškaraca i 3 % žena imalo <65 godina, dosežući 32 % i 16 % među pušačima.[22] Spuštanje granice dobi probira na 60 godina u pušača muškoga spola može biti predmet daljnje diskusije, iako će i tada 13 % bolesnika ponovno biti propušteno. Prema drugom izvještaju, među 530 braće i sestara bolesnika s AAA probir je utvrdio učestalost postojanja AAA od 10%, od čega je trećina njih <65 godina, podupirući činjenicu da je potreban probir braće i sestara tih bolesnika.[23]

Medicinsko zbrinjavanje otkrivenih malih AAA nedostatno je istraženo. U randomiziranoj studiji AARDVARK 224 pacijenta s AAA promjera 30 – 54 mm randomizirano je za primjenu perindoprila, amlodipina ili placeba.[24] Nakon dvije godine praćenja nije uočena razlika u progresiji promjera među ispitivanim grupama, unatoč sniženju vrijednosti arterijskoga tlaka u aktivnim grupama (**Tablica 1**). Važno je naglasiti da je studija uključila samo 10,5 % probranih ispitanika te je bez dostatne jakosti za detekciju malih, ali važnih učinaka na progresiju AAA, upozoravajući na potrebu daljnjeg istraživanja.

Bolest perifernih arterija

U 2016. godini dvije velike randomizirane kliničke studije donijele su važne dokaze u vezi s antitrombotskom terapiju u bolesnika s arterijskom bolesti donjih udova. Studija EUCLID usporedila je tikagrelor u dozi 2 x 90 mg u odnosu prema klopidogrelu u 13 885 bolesnika sa simptomatskom arterijskom bolešću donjih udova (**Tablica 1**).[25] Nakon 30-mjesečnog praćenja nije uočena razlika u primarnome kombiniranom ishodu od kardiovaskularne smrtnosti, infarkta miokarda ili moždanog udara (10,8 % tikagrelor u odnosu prema 10,6 % klopidogrel) te učestalosti događaja na ekstremitetima i stopi znatnih krvarenja (1,6 %). Važno je istaknuti da je navedena analiza i u bolesnika s prethodnom revaskularizacijom potvrdila iste rezultate (**Tablica 1**).[26] Prema tome, u bolesnika s ar-

In type-B AD, standard of care is medical management for uncomplicated cases and thoracic endovascular aortic repair (TEVAR) for complicated ones. However, a recent retrospective study on 338 patients with uncomplicated type-B AD comparing immediate TEVAR (n = 184) to medical therapy (n = 154) showed that 30 day mortality was similar, but medically treated patients had significantly higher mortality (P = 0.01) and aortic-related adverse event rate at 5 year follow-up (P = 0.025).[18] Another retrospective study on 156 patients with uncomplicated acute type B-AD identified an aortic diameter >44 mm as independent predictor of mortality during a median follow-up of 3.7 years; an aortic diameter >44 mm and a false lumen diameter >22 mm were associated with decreased intervention-free survival.[19] These data contribute to the identification of high-risk criteria favouring early TEVAR.

A frequent complication of TEVAR, the post-implantation syndrome (PIS)—defined as fever >38 °C, white blood cells >12.0/nL and C-reactive protein >10 mg/dL within 72 h after TEVAR despite negative blood culture—was reported in 16% of cases with type-B AD; PIS did not affect in-hospital outcome, but was associated with increased rates of major adverse events (death, aortic rupture and need for reintervention) at 4 year follow-up (62.5 vs. 25.9%; P = 0.004).[20]

Ultrasound screening of abdominal aorta aneurysms (AAA) is recommended in all men >65 years (Class I A), and possibly in women >65 years who smoke (Class IIb C).[21] A Finnish study on 585 patients with ruptured AAA, challenged these recommendations, as 21% of men and 3% of women were <65 years, reaching up to 32% and 16%, respectively, among smokers.[22] Decreasing the age of screening to 60 years in male smokers may be then discussed, although still 13% would have been missed. In another report, among 530 siblings of patients with AAA detected by screening, 10% had AAA, one-third being <65 years, supporting current recommendations to screen all siblings of these patients.[23]

Once detected, the medical management of small AAAs is poorly studied. In the randomized AARDVARK trial, 224 patients with AAA diameters of 30–54 mm were randomized to receive perindopril, amlodipine or placebo.[24] After 2 years of follow-up, no difference in terms of diameter progression was found among groups, despite blood pressure decrease in active groups (**Table 1**). Notably, the trial enrolled only 10.5% of screened patients and was under-powered to detect small but important effects on AAA growth rate, highlighting the need for further investigations.

Lower extremity artery disease

In 2016, two large RCTs provided important evidence regarding antithrombotic therapy in patients with lower extremity artery disease (LEAD). The EUCLID trial compared ticagrelor 90 mg b.i.d. vs. clopidogrel in 13 885 patients with symptomatic LEAD (**Table 1**).[25] After 30 months of follow-up, no differences were observed in the primary end-point, a composite of CV death, MI, or stroke (10.8% ticagrelor vs. 10.6% clopidogrel), and in the rates of limb events and major bleeding (1.6%). Importantly, the pre-specified analysis of patients with prior revascularization confirmed the main results (**Table 1**).[26] Therefore, in LEAD patients without recent (<30 days) revascularization, clopidogrel appears as effective as ticagrelor.

terijskom bolešću donjih udova bez nedavne (<30 dana) revaskularizacije klopidogrel je jednako učinkovit kao tikagrelor.

Vorapaxar, antagonist proteaza-aktiviranog receptora-1, dokazao se učinkovitim u smanjenju akutne ishemije donjih udova među 3787 bolesnika sa simptomatskom arterijskom bolešću nogu, koji su uključeni u studiju TRA2°P, pri čemu je trogodišnji rizik od akutne ishemije smanjen 42 % u odnosu prema placebu uz acetilsalicilatnu kiselinu i/ili tienopiridin (2,3 % prema 3,9 %; P = 0,006) (**Tablica 1**).[27] Registrirana dobrobit ne ovisi o etiologiji akutne ishemije donjih udova i nema povećanja ozbiljnoga krvarenja. Vorapaxar je također reducirao učestalost periferne revaskularizacije (15,4 % prema 19,3 %; P = 0,003) među 5845 bolesnika s poznatom arterijskom bolesti donjih udova, uz povećanje umjerenog, ali ne ozbiljnog krvarenja (**Tablica 1**).[28] Viša godišnja učestalost akutne ishemije donjih udova u studiji TRA2°P u usporedbi sa studijom EUCLID (1,2 % prema 0,8 %) pokazuje da je studija TRA2°P uključila bolesnike s višim rizikom od događaja na donjim udovima. Kombinacija acetilsalicilne kiseline i vorapaxara može biti mogućnost za bolesnike s povećanim rizikom od akutne ishemije donjih udova, npr. pušači te bolesnici koji imaju kiruršku revaskularizaciju (graft), ako je učestalost krvarenja niska.

Što se tiče revaskularizacije, nedavno su prikazani trogodišnji rezultati studije IN.PACT SFA (**Tablica 1**).[29] Studija je u omjeru 2 : 1 uključila 331 bolesnika s femoropoplitealnim lezijama u liječenje primjenom DEB-a (engl. *drug-eluting balloon*) ili standardnom balonskom dilatacijom (PTA). U tri godine terapija DEB-om bila je povezana s mnogo većom primarnom prohodnošću (69,5 % prema 45,1 %; P < 0,001) i izostankom klinički uvjetovane revaskularizacije ciljne lezije (CD-TRL) (84,5 % prema 70,4 %; P < 0,001) u nedostatku kasnoga zaostalog fenomena. Ipak, ukupni rezultati s DEB-om i dalje su ograničeni te se ne može odrediti učinak skupine na osnovi povoljnih rezultata ove studije. Petogodišnji rezultati studije Zilver PTX, koja je uključila 474 bolesnika s femoropoplitealnom arterijskom lezijom i primarnom implantacijom paklitaksel-otpuštajućeg stenta (PES) u usporedbi s PTA, također je objavljena 2016. godine.[30] Povoljni rezultati PES-a održani su tijekom pet godina; ukupna PES grupa (primarna i kontrolna) bila je superiorna standardnom zbrinjavanju (PTA+ BMS) u uvjetima primarne prohodnosti i izostanka klinički uvjetovane revaskularizacije ciljne lezije (**Tablica 1**). Obećavajući su rezultati objavljeni glede novog everolimus-otpuštajućeg bioresorbabilnog vaskularnog *scaffolda* za liječenje vanjske ilijačne i površinske femoralne arterije u studiji ESPRIT I.[31]

Venski tromboembolizam

Nakon idiopatske pojave venskog tromboembolizma klinička procjena ponovnog VTE-a i rizika od krvarenja mogu biti korisni u procjeni trajanja antikoagulantne terapije. Nedavni postantikoagulantni D-dimer model[32] i DAMOVES[33] bodovna ljestvica (**Tablica 2**) dodatak su postojećim modelima, gdje još uvijek uglavnom nedostaje procjena bazirana na prospektivnim studijama. Nedavno je bodovna ljestvica HERDOO (**Tablica 2**) prospektivno validirana u 2779 bolesnika; antikoagulantna terapija može se sa sigurnošću isključiti u žena s prvim neprovocirajućim događajem venskog tromboembolizma koje se prezentiraju rezultatom <2 prema HERDOO bodovnoj ljestvici.[34] Integracija ljestvica mogućnosti recidiva VTE-a i ljestvice rizika od krvarenja omogućuje individualizirani pristup, ali dostupne ljestvice za procjenu rizika od krvarenja nisu dovoljno uspješne u VTE-u. Nedavno razvijena VTE-BLEED bodovna lje-

Vorapaxar, a protease-activated receptor-1 antagonist, proved effective in reducing acute limb ischaemia (ALI) among 3787 patients with qualifying symptomatic LEAD enrolled in the TRA2°P trial, reducing the 3 year risk of ALI by 42% vs. placebo on top of aspirin and/or a thienopyridine (2.3% vs. 3.9%; *P* = 0.006) (**Table 1**).[27] The benefit was consistent across all aetiologies of ALI, without increase in severe bleedings. Vorapaxar also reduced peripheral revascularizations (15.4% vs. 19.3%; *P* = 0.003) among the 5845 patients with known LEAD, with an increase in moderate but not in severe bleedings (**Table 1**).[28] The higher annualized rate of ALI in TRA2°P vs. EUCLID (1.3% vs. 0.8%) indicates that TRA2°P enrolled patients at higher risk of limb events. The combination of aspirin and vorapaxar might represent an option in patients at high risk of ALI, i.e. smokers and surgical graft recipients, provided that bleeding risk is low.

Regarding revascularization, the 3 year results of the IN.PACT SFA trial were recently reported (**Table 1**).[29] This trial randomized in 2:1 fashion 331 patients with femoro-popliteal lesions to treatment with drug-eluting balloon (DEB) or standard balloon (PTA). At 3 years, DEB continued to be associated with significantly higher primary patency (69.5% vs. 45.1%; *P* < 0.001) and freedom from clinically driven target-lesion revascularization (CD-TLR) (84.5% vs. 70.4%; *P* < 0.001), in the absence of late catch-up phenomenon. Nevertheless, overall results on DEB continue to be limited, and no class effect can be postulated based on the favourable results of this trial. The 5 year results of the Zilver PTX trial, randomizing 474 patients with femoro-popliteal artery lesions to primary implantation of a paclitaxel-eluting stent (PES) vs. PTA, were also reported in 2016.[30] The favourable results of PES were sustained through 5 years; the overall PES group (primary + provisional) was superior to standard care (PTA + provisional BMS) in terms of primary patency and of freedom from CD-TLR (**Table 1**). Promising results were reported regarding a novel everolimus-eluting bioresorbable vascular scaffold for the treatment of external iliac and superficial femoral artery in the ESPRIT I study.[31]

Venous thromboembolism

Following an idiopathic VTE event, clinical prediction rules for recurrence and bleeding risk may be useful to decide the duration of anticoagulation. The recent post-anticoagulation D-dimer model[32] and DAMOVES [33] score (**Table 2**) add on to the available models, mostly still missing validation in prospective studies. Very recently, the HERDOO score (**Table 2**) was prospectively validated in 2779 patients; anticoagulation could safely be discontinued in women with a first unprovoked VTE who presented with a HERDOO score <2.[34] The integration of recurrence and bleeding risk scores may allow a personalized management, but available bleeding scores have largely been unsuccessful in VTE. The recently developed VTE-BLEED accurately predicted 30 day bleeding risk in patients on dabigatran and warfarin, deserving further evaluation.[35]

Unprovoked VTE may be an early sign of cancer. It remains unclear whether a subgroup of high-risk patients with unprovoked VTE could potentially benefit from a more extensive screening strategy. The Screening for Occult Malignancy in Patients with Idiopathic Venous Thromboembolism (SOME) trial showed that age, smoking status, and prior provoked VTE

TABLE 2. Characteristics included in recurrence and bleeding scores for patients suffering unprovoked venous thromboembolism.

	HER-DOO[33]	DAMOVES[32]	Post D-dimer model*[31]
Leg Hyperpigmentation, Edema or Redness [HER]	1		
D-Dimer levels [D]	1 (>250 ug/L)	5 (abnormal)	2
Obesity [O]	1 (BMI≥ 30)	2.5 (BMI> 30)	
Age [O] [A]	1 (≥65 years)	16 (1090 years)	0.98
Genetic thrombophilia [M]		5	
Varicose veins [V]		2.5	
Factor VIII activity [E]		1.510 (50%400%)	
Male sex [S]		2	2
Proximal vein thrombosis or pulmonary embolism			5
Time between cessation of anticoagulation and D-dimer measurement (days)			0.74
Cut-off value for score	≥2	≥11.5	–

Numbers represent the value attributed to each characteristic in the scores; capital letters in brackets represent the letter chosen for the score acronym.

**Numbers represent hazard ratios and not score values.

stvica točno predviđa 30-dnevni rizik od krvarenja u bolesnika na dabigatranu i varfarinu te zaslužuje daljnju procjenu.[35]

Idiopatska pojava VTE-a može biti rani znak maligne bolesti. Ostaje nejasno bi li podskupina visokorizičnih bolesnika s VTE-om imala koristi od šire strategije probira. Studija SOME (engl. *The Screening for Occult Malignancy in Patients with Idiopathic Venous Thromboembolism*) pokazala je da dob, pušenje te prethodna epizoda VTE mogu biti važni prediktori skrivene malignosti u bolesnika s prvom epizodom neprovocirajuće VTE (HR 3,33; P < 0,001).[36]

I dalje je predmet rasprave zahtijeva li izolirana distalna duboka venska tromboza (DVT) antikoagulantnu terapiju. Nedavna studij aCACTUS uključila je niskorizične ambulantne bolesnike (bez aktivne maligne bolesti ili prethodnog VTE-a) s prvom epizodom izolirane distalne DVT, koji su primali supkutani niskomolekularni heparin (LMWH) ili placebo 6 tjedana.[37] Učestalost simptomatske VTE nije bila različita između dviju skupina (3 % prema 5 %; P = 0,54), dok je rizik od krvarenja bio viši (4 % prema 0 %; P = 0,03) (**Tablica 1**). Iako je studija bila u velikoj mjeri nedovoljno snažna s obzirom na nisku stopu događaja, ona ipak upućuje na to da svi niskorizični ambulantni bolesnici sa simptomatskom izoliranom distalnom DVT ne bi trebali dobiti punu dozu LMWH-a. Alternativne strategije, poput profilaktične primjene LMWH-a i izravnih oralnih antikoagulancija, trebale bi biti predmet daljnjeg istraživanja.

Nakon studija velikih razmjera u III. fazi kliničkog istraživanja, podatci iz kliničke prakse potvrđuju sigurnost i učinkovitost novih oralnih antikoagulancija kao alternativne strategije standardnoj antikoagulantnoj terapiji u širokoj skupini bolesnika. Nedavni podatci ističu povećano vaginalno i teže menstrualno krvarenje u bolesnica liječenih anti-Xa lijekovima.[38] Ipak, većina se bolesnika može liječiti konzervativno. Među reverznim lijekovima, anti-Xa andexanet snizuje aktivnost antifaktora Xa u akutno krvarećih bolesnika i osigurava učinkovitu hemostazu u 79 % slučajeva.[39]

U bolesnika koji imaju kontraindikaciju za antikoagulanciju, dokazi za primjenu vena kava filtra ostaju nedostatni.

may be important predictors of occult cancer in patients with first unprovoked VTE (combined effect HR 3.33; $P < 0.001$).[36]

Whether isolated distal deep vein thrombosis (DVT) requires anticoagulation is still debated. The recent CACTUS trial randomized low-risk outpatients (without active cancer or previous VTE) with a first isolated distal DVT to receive subcutaneous low-molecular-weight heparin (LMWH) or placebo for 6 weeks.[37] Rates of symptomatic VTE were not different between the two groups (3% vs. 5%; $P = 0.54$), while bleeding risk was higher (4% vs. 0%; $P = 0.03$) (**Table 1**). Although the trial was largely underpowered given the low event rates, it suggests that not all low-risk outpatients with symptomatic isolated distal DVT should receive full-dose LMWH. Alternative strategies such as prophylactic LMWH doses and direct oral anticoagulants (DOAC) need to be investigated.

Following large-scale phase-III clinical trials, real-world data confirm safety and effectiveness of DOACs as alternative to standard anticoagulation in a broad range of patients. Recent data pointed out to increased vaginal and heavy menstrual bleeding in women treated with anti-Xa drugs.[38] However, most of patients could be treated conservatively. Among reversal agents, the antiXa andexanet reduced anti-factor Xa activity in acutely bleeding patients and assured effective haemostasis in 79% of cases.[39]

In patients with contraindication to anticoagulation, evidence for inferior vena cava filter use remains elusive. Recent data showed that, in non-cancer acute VTE patients, filter use was associated with a significant reduction in 30 day mortality only in case of contraindication to anticoagulation because of bleeding (HR, 0.68).[40] However, risk of subsequent DVT increased by 135%.

Pulmonary embolism (PE) is part of the differential diagnosis of syncope; a recent prospective study on 560 patients hospitalized for syncope reported a 17.3% prevalence of PE in this population, supporting the inclusion of PE imaging in the diagnostic workup of syncope.[41]

Nedavni podatci pokazuju da je u bolesnika s akutnom VTE, bez maligne bolesti, upotreba filtra bila povezana sa znatnim sniženjem 30-dnevne smrtnosti, samo u slučajevima kontraindikacije za antikoagulancije zbog krvarenja (HR, 0,68).[40] No, rizik od posljedične VTE povećao se za 135 %.

Plućna embolija (PE) dio je diferencijalne dijagnoze sinkope; nedavna prospektivna studija na 560 bolesnika hospitaliziranih zbog sinkope prijavila je 17,3% prevalencije PE u toj populaciji, potičući uključivanje dijagnostičkog probira za PE u dijagnozi sinkope.[41]

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